REMARKS

The application has been amended and is believed to be in condition for allowance.

Amendments to the Disclosure

Claims 11 and 13 are amended to sharpen the claim language claiming the invention. The amendments to claim 11 is directed to the elected Group I drawn to a method for preparing a non-pathogenic amoeba vesicle. The amendment to claim 13 is directed to the unelected Group II drawn to an isolated non-pathogenic amoeba vesicle, respectively (hence, claim 13 is indicated as "withdrawn - currently amended"). The amendments find support in the specification and the drawing figures as originally filed (e.g., page 2, lines 19-22; page 11, lines 26-28; page 4, lines 3-5; and page 6, lines 30-32).

New claims 20-36 are introduced to further distinguish the invention from the prior art. New claims 20-36 are directed to the elected Group I drawn to a method for preparing a non-pathogenic amoeba vesicle.

Support for new claims 20, 24, 25, 29, 33, and 34 can be found at least at page 4, lines 3-5 and page 6, lines 30-32 of the specification as filed. Support for new claims 21-23 and 30-32 can be found at least at page 6, lines 12-25 of the application as filed. Support for new claims 26, and 35 can be found at least at page 4, lines 12-18 and page 6, lines 9-12 of the application as filed. Support for new claims 27, and 36 can

be found at least at page 5, lines 2-10 of the application as filed. Support for new claim 28 can be found, at least, on page 4, lines 14-16 of the application as filed.

None of the foregoing amendments to the claims introduce new matter.

Formal Matters - Objections to the Specification

The Official Action objected to the specification based on various informalities.

In reply, the specification is amended responsive to the Official Action's suggestions spanning pages 4 and 5.

As to the references listed in the specification, Applicant does no intend that this list constitute an Information Disclosure Statement.

Withdrawal of the objections to the specification is respectfully requested.

Formal Matters - Objections to the claims

The Official Action objected to claim 12 as failing to further limit the subject matter of a parent claim.

In response, claim 11 has been amended in a manner believed to overcome the Official Action's objection. Withdrawal of the objection to the claims is respectfully requested.

Formal Matters - Section 112, second paragraph

The Official Action rejected claims 11 and 12 under 35 USC 112, second paragraph as being indefinite as to whether the vesicle may or may not contain Hoechst 33342.

In response, claim 11 is amended in a manner believed to be definite. Claim 11 allows for a vesicle that is a *Dictyostelium discoideum* vesicle, as long as the *Dictyostelium discoideum* vesicle does not contain Hoechst 33342. That is, the only vesicles that are excluded are *Dictyostelium discoideum* vesicles which also include Hoechst 33342.

The foregoing amendment to claim 11 is also believed to overcome the Official Action's objection to claim 12.

Withdrawal of the rejections under 35 USC 112, second paragraph is thereby respectfully requested.

Substantive Issues - Section 103

The Official Action rejected claim 12 under 35 USC 103(a) as being unpatentable over Tatischeff et al., CMLS Cellular and Molecular Life Sciences, Vol. 54, pages 475-487, 1998 (hereinafter "TATISCHEFF 1998").

The Official Action rejected claim 11 under 35 USC 103(a) as being unpatentable over TATISCHEFF 1998 and John Tyler Bonner, "The Cellular Slime Molds", second edition 1967 (hereinafter "BONNER").

The rejections are respectfully traversed for at least the reasons that follow.

It is firstly noted that claims 11 and 12 are amended to clarify the recitation of the invention. It is respectfully submitted that none of the applied references, individually or in combination, teach or suggest the combination of steps of

culturing a non-pathogenic amoeba cell in a culture medium comprising a molecule of interest under conditions sufficient to allow the non-pathogenic amoeba cell to release vesicles, and recovering a vesicle released by the non-pathogenic amoeba cell, wherein the vesicle contains the molecule of interest, and wherein the molecule of interest is selected from the group consisting of i) a therapeutic molecule, ii) an imaging agent, and iii) a diagnostic agent, with the proviso that the vesicle is not a Hoechst 33342-containing *Dictyostelium discoideum* vesicle.

The Official Action asserts that it would have been *prima facie* obvious to modify the method of TATISCHEFF by culturing *Dictyostelium discoideum* cells with anthracyclines and other cytotoxic drugs to determine if such compounds would be enclosed in vesicles that would then be shed into the extra-cellular medium.

However, the Official Action concedes that TATISCHEFF fails to teach culturing *D. discoideum* with any other molecule, and only offers BONNER as teaching that *D. discoideum*, as well as *Dictyostelium lacteum*, *Dictyostelium minutum*, *Dictyostelium mucoroides*, and *Dictyostelium purpurem* are all slime molds that exist as single cells but can aggregate and form fruiting bodies.

The Official Action's argument hinges on the assertion that the proposed modification would have been "obvious to try" thereby to produce the instantly claimed method because TATISCHEFF "specifically recognized the problem or need in the

art to solve the problem" of determining if cells that are resistant to other xenobiotics are resistant using the method of shedding vesicles containing the xenobiotics. The Official Action alleges that given the known problem to be solved, given the known conventional and successful techniques for solving the problem, and "given that TATISCHEFF provides a specific identified, predictable, potential solution" to the recognized problem, the variation of the technique of TATISCHEFF as proposed is obvious.

Applicants respectfully disagree for at least the following reasons.

I. TATISCHEFF DID NOT RECOGNIZE THE PROBLEM TO BE SOLVED BY AMENDED CLAIM 11.

TATISCHEFF discloses a study aiming at unraveling the resistance and detoxification mechanisms *D. discoideum* cellular resistance:

> Searching for a new resistance mechanism to explain the high endogenous resistance of D. discoideum cells, we observed that...
> (Page 477, right column, 2nd paragraph)

> The present observation of a cellular traffic targeting HO342 into the extracellular medium by means of vesicles indicates a new possible mechanism for the high cellular resistance of *Dd* cells against this DNA targeted vital stain.
> (Paragraph bridging pages 485 and 486).

In addition, in TATISCHEFF, HO342 is merely used as a staining molecule useful for following the detoxification pathway in *D. discoideum*.

In stark contrast, amended claim 11 pertains to the preparation of *D. discoideum* vesicles for delivering a molecule of interest to a eukaryotic target cell, wherein said vesicle comprises a therapeutic molecule, an imaging agent or a diagnostic agent

TATISCHEFF neither teaches nor suggest that *D. discoideum* vesicles might be useful for delivering a molecule of interest to a eukaryotic target cell, and thus find use in therapeutic, diagnostic and medical imaging applications. Therefore, TATISCHEFF did not recognize the problem to be solved by amended claim 11, as alleged by the Official Action.

II. THERE WAS NO REASONABLE EXPECTATION OF SUCCESS IN VIEW OF TATISCHEFF.

TATISCHEFF discloses that, in presence of the DNA-dye HO342, *D. discoideum* cells produce extracellular vesicles containing HO342 which contribute to the elimination of HO342 (page 485, left column, 2nd paragraph).

However, TATISCHEFF discloses:

(a) a new, yet unidentified mechanism explaining the cellular resistance of *D. discoideum* (see, e.g. abstract and page 485, left column, last paragraph); and

(b) one single example of molecule, namely the HO342 DNA-dye, that can be internalized into *D. discoideum* vesicles.

The authors of the TATISCHEFF article thus conclude that this mechanism cannot be extended to molecules different from HO342 without further experimentation being carried out:

> However, before being able to extend such a mechanism mediated by vesicular traffic to detoxification of other xenobiotics, experiments should be carried out with anthracyclines and other cytotoxic drugs binding to targets other than nucleic acids.
> (Page 486, left column, 1st paragraph)

In view of this teaching, one skilled in the art could not predict whether *D. discoideum* vesicles comprising a therapeutic molecule, an imaging agent or a diagnostic agent different from HO342 could be prepared. In other words, assuming that the skilled in the art had tried to prepare a vesicle comprising a molecule different from HO342, he would not have had a reasonable expectation of success.

Further, HO342 is a molecule binding to nucleic acids; that is, a hydrophilic molecule targeting an A-T cluster on DNA. In addition, HO342 is the substrate of a multidrug resistance protein, i.e. of a protein playing a role in multidrug resistance mechanisms. The capacity of a xenobiotic to be a substrate of a multidrug resistance protein cannot be presumed.

How *D. discoideum* cells would have been considered by one of skill as a molecule different from HO342 could not have been presumed. Indeed, one of skill familiar with the content of

multidrug resistance mechanisms in tumoral cells, a xenobiotic gives rise to a specific resistance mechanism depending on its physical and chemical properties.

Therefore, the skilled person would have had no reasonable expectation that the method described in TATISCHEFF could work with molecules different from HO342.

In contrast, the present application teaches that vesicles comprising various molecules that do not bind to DNA, e.g., hypericin, doxorubicin and an oligodeoxynucleotide, can be prepared (see e.g, Example 9 from page 9, line 29 to page 37, line 21 of the application as filed). This result was in no way predictable in view of TATISCHEFF.

III. BONNER DOES NOT ADD ANYTHING TO THE TEACHING OF TATISCHEFF.

BONNER merely provides a list of amoeba species. It neither teaches nor suggests that amoeba species may be useful for preparing vesicles for delivering a molecule of interest to a eukaryotic target cell.

IV. CONCLUSION.

Based at least on the foregoing, it is respectfully submitted that claim 11 is non-obvious in view of TATISCHEFF alone, nor in combination with BONNER.

V. CLAIMS 12 AND 20-36

Claims 12 and 20-36 depend, directly or indirectly, from claim 11. Therefore, it is respectfully submitted that

claims 12 and 20-36 are patentable over the applied references at least based on the arguments set forth hereabove in connection with claim 11.

For example, claims 20-23 and 29-32 recite that the molecule of interest is a therapeutic molecule. As set forth hereabove, TATISCHEFF aims at unraveling detoxification mechanisms in *D. discoideum*, and neither teaches nor suggests a therapeutic use for the prepared vesicles. It is thus not *prima facie* obvious to replace the HO342 DNA-dye with a therapeutic molecule in view of a therapeutic use of the vesicles.

Claims 26 and 35 recite that the molecule of interest is a small chemical molecule, a small organic compound, a small inorganic compound or a nucleic acid. As explained hereabove, TATISCHEFF only demonstrates that a *D. discoideum* vesicle comprising a molecule binding to nucleic acids could be prepared. It is thus not *prima facie* obvious to replace the HO342 DNA-dye with a small chemical molecule, a small organic compound, a small inorganic compound or a nucleic acid.

V. CLAIMS 13 AND 14

Based at least on the foregoing in relation to claims 11 and 12, it is also respectfully submitted that the prior art fails to contemplate the pathogenic amoeba vesicle as recited by withdrawn claims 13 and 14. Accordingly, rejoinder of the withdrawn claims 13 and 14 is respectfully requested.

VII. CONCLUSION

From the foregoing, it will be apparent that Applicants have fully responded to the July 2, 2009 Official Action and that the claims as presented are patentable. In view of this, Applicants respectfully request reconsideration of the claims, as presented, and their early passage to issue.

In order to expedite the prosecution of this case, the Examiner is invited to telephone the attorney for Applicants at the number provided below if the Examiner is of the opinion that further discussion of this case would be helpful in advancing prosecution.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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